REMARKS

The foregoing amendments amend the specification to reflect the 371 status. In addition, the multiple dependencies of the claims have been removed in order to remove the improper multiple dependencies and to reduce the PTO filing fee.

Attached hereto is a marked-up version of the changes made to the specification and claims by the current amendment. The attached pages are captioned "**Version with markings to show changes made**".

Favorable action on the merits is solicited.

Respectfully submitted,

Kunihiko IIZUKA et al.

By _____
Warren M. Cheek, Jr.
Registration No. 33,367
Attorney for Applicants

WMC/dlk
Washington, D.C. 20006-1021
Telephone (202) 721-8200
Facsimile (202) 721-8250
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SPECIFICATION

AGENT FOR PROPHYLAXIS AND TREATMENT OF INTERSTITIAL PNEUMONIA AND PULMONARY FIBROSIS

This application is a 371 of PCT/JP00/01728 filed March 21, 2000.

Technical Field

The present invention relates to an agent for the prophylaxis and treatment of interstitial pneumonia and pulmonary fibrosis. More specifically, the present invention relates to an agent for the prophylaxis and treatment of interstitial pneumonia and pulmonary fibrosis, which comprises a compound having a Rho kinase inhibitory activity as an active ingredient.

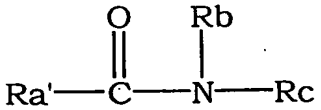
Background Art

Interstitial pneumonia is an inflammation of lung stroma, which means an inflammation of alveolar wall and peripheral supporting tissue. While it includes local one and diffuse one, interstitial pneumonia generally means diffuse interstitial pneumonia, including acute type and chronic type. Histologically, it is classified into five types of UIP (usual or classical interstitial pneumonia), BIP (obstructive bronchiolar interstitial pneumonia), DIP (desquamative interstitial pneumonia), LIP (lymphoid interstitial pneumonia) and GIP (giant cell interstitial pneumonia). Those having an unknown cause are called idiopathic interstitial pneumonia (IIP) in Japan and idiopathic pulmonary fibrosis (IPF) in US and Europe. Those having a known cause include pneumoconiosis, hypersensitivity pneumonitis, radiation pneumonitis, infection disease and the like. The disease sometimes accompanies a systemic dusease, such as sarcoidosis, histiocytosis X, collagen disease and the like. Clinically, dry coughing, exertional dyspnea, fever, clubbing of finger, cyanosis and the like are observed. One associated with systemic disease shows other systemic symptoms. The disease shows Velcro rale (fine crackle) by chest auscultation, ground glass opacity in an early stage, then fine particle-like shadow, and orbicular shadow and honeycomb shadow as the disease progresses, by chest X-ray image. By ventilatory function test,

(Amended)

addition salt thereof.

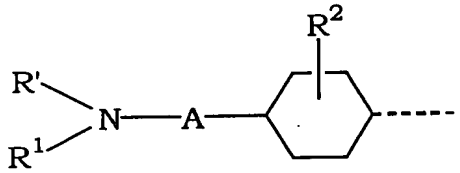
3. The agent for the prophylaxis and treatment of interstitial pneumonia and pulmonary fibrosis of claim 1 ~~or claim 2~~, wherein the compound having a Rho kinase inhibitory activity is an amide compound of the following formula (I')



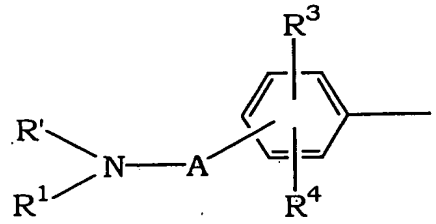
(I')

wherein

Ra' is a group of the formula



(a')



(b')

wherein

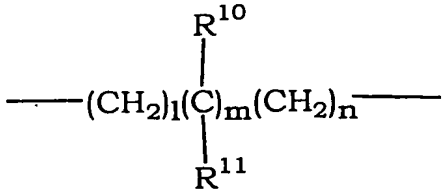
R' is hydrogen, alkyl, or cycloalkyl, cycloalkylalkyl, phenyl or aralkyl, which optionally has a substituent on the ring,

R^1 is hydrogen, alkyl, or cycloalkyl, cycloalkylalkyl, phenyl or aralkyl, which optionally has a substituent on the ring, or R' and R^1 in combination form, together with the adjacent nitrogen atom, a group forming a heterocycle optionally having, in the ring, oxygen atom, sulfur atom or optionally substituted nitrogen atom,

R^2 is hydrogen or alkyl,

R^3 and R^4 are the same or different and each is hydrogen, alkyl, aralkyl, halogen, nitro, amino, alkylamino, acylamino, hydroxy, alkoxy, aralkyloxy, cyano, acyl, mercapto, alkylthio, aralkylthio, carboxy, alkoxycarbonyl, carbamoyl, alkylcarbamoyl or azide, and

A is a group of the formula



(e)

wherein R^{10} and R^{11} are the same or different and each is hydrogen, alkyl, haloalkyl, aralkyl, hydroxyalkyl, carboxy or alkoxycarbonyl, or R^{10} and R^{11} show a group which forms cycloalkyl in combination and l, m and n are each 0 or an integer of 1-3,

Rb is a hydrogen, an alkyl, an aralkyl, an aminoalkyl or a mono- or dialkylaminoalkyl; and

Rc is an optionally substituted heterocycle containing nitrogen,

an isomer thereof and/or a pharmaceutically acceptable acid addition salt thereof.

4. The agent for the prophylaxis and treatment of interstitial pneumonia and pulmonary fibrosis of claim 1, wherein the compound having a Rho kinase inhibitory activity is a compound selected from the group consisting of (+)-trans-4-(1-aminoethyl)-1-(4-pyridylcarbamoyl)cyclohexane, (+)-trans-N-(1H-pyrrolo[2,3-b]pyridin-4-yl)-4-(1-aminoethyl)cyclohexanecarboxamide, (R)-(+)-N-(4-pyridyl)-4-(1-aminoethyl)benzamide and (R)-(+)-N-(1H-pyrrolo[2,3-b]pyridin-4-yl)-4-(1-aminoethyl)benzamide, and/or a pharmaceutically acceptable acid addition salt thereof.

5. The agent for the prophylaxis and treatment of interstitial pneumonia and pulmonary fibrosis of claim 1, wherein the compound

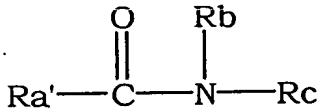
a mono- or dialkylaminoalkyl; and

Rc is an optionally substituted heterocycle containing nitrogen,

an isomer thereof and/or a pharmaceutically acceptable acid addition salt thereof.

(Amended)

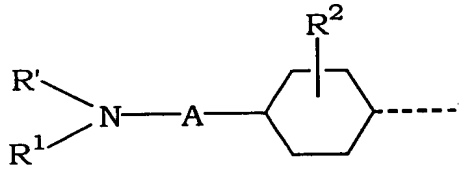
8. The pharmaceutical composition for the prophylaxis and treatment of interstitial pneumonia and pulmonary fibrosis of claim 6 ~~or claim 7~~, wherein the compound having a Rho kinase inhibitory activity is an amide compound of the following formula (I')



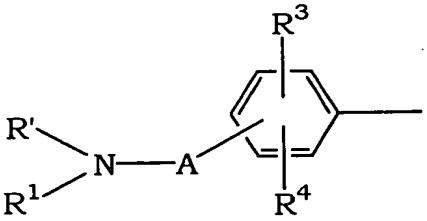
(I')

wherein

Ra' is a group of the formula



(a')



(b')

wherein

R' is hydrogen, alkyl, or cycloalkyl, cycloalkylalkyl, phenyl or aralkyl, which optionally has a substituent on the ring,

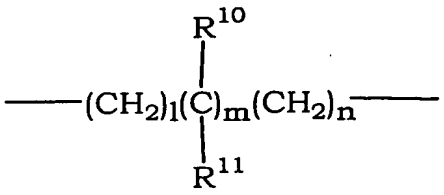
R^1 is hydrogen, alkyl, or cycloalkyl, cycloalkylalkyl, phenyl or aralkyl, which optionally has a substituent on the ring, or R' and R^1 in combination form,

together with the adjacent nitrogen atom, a group forming a heterocycle optionally having, in the ring, oxygen atom, sulfur atom or optionally substituted nitrogen atom,

R^2 is hydrogen or alkyl,

R^3 and R^4 are the same or different and each is hydrogen, alkyl, aralkyl, halogen, nitro, amino, alkylamino, acylamino, hydroxy, alkoxy, aralkyloxy, cyano, acyl, mercapto, alkylthio, aralkylthio, carboxy, alkoxycarbonyl, carbamoyl, alkylcarbamoyl or azide, and

A is a group of the formula



(e)

wherein R^{10} and R^{11} are the same or different and each is hydrogen, alkyl, haloalkyl, aralkyl, hydroxyalkyl, carboxy or alkoxycarbonyl, or R^{10} and R^{11} show a group which forms cycloalkyl in combination and l, m and n are each 0 or an integer of 1-3,

Rb is a hydrogen, an alkyl, an aralkyl, an aminoalkyl or a mono- or dialkylaminoalkyl; and

Rc is an optionally substituted heterocycle containing nitrogen,

an isomer thereof and/or a pharmaceutically acceptable acid addition salt thereof.

9. The pharmaceutical composition for the prophylaxis and treatment of interstitial pneumonia and pulmonary fibrosis of claim 6, wherein the compound having a Rho kinase inhibitory

thienylmethyl,

W is alkylene,

Q^2 is hydrogen, halogen, hydroxy or aralkyloxy,

X is alkylene,

Q^3 is hydrogen, halogen, hydroxy, alkoxy, nitro, amino, 2,3-dihydrofuryl or 5-methyl-3-oxo-2,3,4,5-tetrahydropyridazin-6-yl;

and Y is a single bond, alkylene or alkenylene, and

in the formula (C),

a broken line is a single bond or a double bond, and

R^5 is hydrogen, hydroxy, alkoxy, alkoxycarbonyloxy, alkanoyloxy or aralkyloxycarbonyloxy;

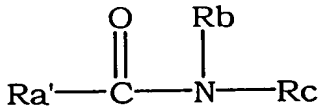
Rb is a hydrogen, an alkyl, an aralkyl, an aminoalkyl or a mono- or dialkylaminoalkyl; and

Rc is an optionally substituted heterocycle containing nitrogen,

an isomer thereof and/or a pharmaceutically acceptable acid addition salt thereof.

(Amended)

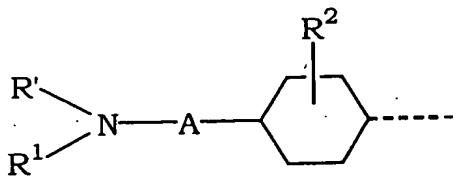
13. The method of the prophylaxis and treatment of interstitial pneumonia and pulmonary fibrosis of claim 11 ~~or claim 12,~~ wherein the compound having a Rho kinase inhibitory activity is an amide compound of the following formula (I')



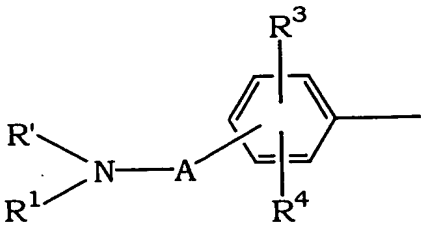
(I')

wherein

Ra' is a group of the formula



(a')



(b')

wherein

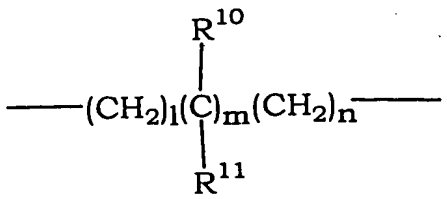
R' is hydrogen, alkyl, or cycloalkyl, cycloalkylalkyl, phenyl or aralkyl, which optionally has a substituent on the ring,

R^1 is hydrogen, alkyl, or cycloalkyl, cycloalkylalkyl, phenyl or aralkyl, which optionally has a substituent on the ring, or R' and R^1 in combination form, together with the adjacent nitrogen atom, a group forming a heterocycle optionally having, in the ring, oxygen atom, sulfur atom or optionally substituted nitrogen atom,

R^2 is hydrogen or alkyl,

R^3 and R^4 are the same or different and each is hydrogen, alkyl, aralkyl, halogen, nitro, amino, alkylamino, acylamino, hydroxy, alkoxy, aralkyloxy, cyano, acyl, mercapto, alkylthio, aralkylthio, carboxy, alkoxycarbonyl, carbamoyl, alkylcarbamoyl or azide, and

A is a group of the formula



(e)

wherein R^{10} and R^{11} are the same or different and each is hydrogen, alkyl, haloalkyl, aralkyl, hydroxyalkyl,

aralkyloxy, aminoalkyl, hydroxyalkyl, alkanoyloxy-alkyl, alkoxycarbonylalkyl, α-aminobenzyl, furyl, pyridyl, phenyl, phenylamino, styryl or imidazopyridyl,

Q^1 is hydrogen, halogen, hydroxy, aralkyloxy or thienylmethyl,

W is alkylene,

Q^2 is hydrogen, halogen, hydroxy or aralkyloxy,

X is alkylene,

Q^3 is hydrogen, halogen, hydroxy, alkoxy, nitro, amino, 2,3-dihydrofuryl or 5-methyl-3-oxo-2,3,4,5-tetrahydropyridazin-6-yl;

and Y is a single bond, alkylene or alkenylene, and

in the formula (c),

a broken line is a single bond or a double bond, and

R^5 is hydrogen, hydroxy, alkoxy, alkoxycarbonyloxy, alkanoyloxy or aralkyloxycarbonyloxy;

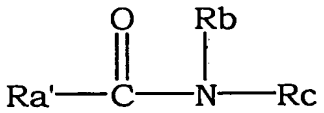
Rb is a hydrogen, an alkyl, an aralkyl, an aminoalkyl or a mono- or dialkylaminoalkyl; and

Rc is an optionally substituted heterocycle containing nitrogen,

an isomer thereof and/or a pharmaceutically acceptable acid addition salt thereof.

(amended)

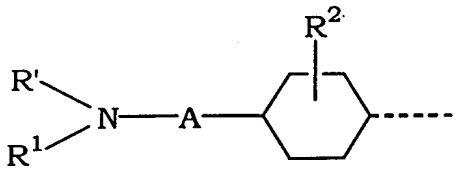
18. The use of claim 16 ~~or claim 17~~, wherein the compound having a Rho kinase inhibitory activity is an amide compound of the following formula (I')



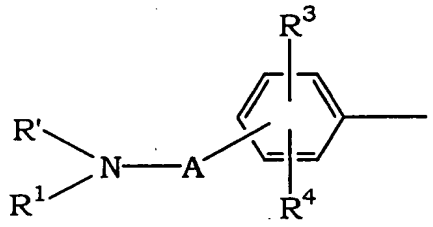
(I')

wherein

Ra' is a group of the formula



(a')



(b')

wherein

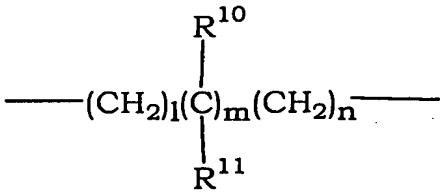
R' is hydrogen, alkyl, or cycloalkyl, cycloalkylalkyl, phenyl or aralkyl, which optionally has a substituent on the ring,

R^1 is hydrogen, alkyl, or cycloalkyl, cycloalkylalkyl, phenyl or aralkyl, which optionally has a substituent on the ring, or R' and R^1 in combination form, together with the adjacent nitrogen atom, a group forming a heterocycle optionally having, in the ring, oxygen atom, sulfur atom or optionally substituted nitrogen atom,

R^2 is hydrogen or alkyl,

R^3 and R^4 are the same or different and each is hydrogen, alkyl, aralkyl, halogen, nitro, amino, alkylamino, acylamino, hydroxy, alkoxy, aralkyloxy, cyano, acyl, mercapto, alkylthio, aralkylthio, carboxy, alkoxycarbonyl, carbamoyl, alkylcarbamoyl or azide, and

A is a group of the formula



(e)

wherein R^{10} and R^{11} are the same or different and each

is hydrogen, alkyl, haloalkyl, aralkyl, hydroxyalkyl, carboxy or alkoxycarbonyl, or R^{10} and R^{11} show a group which forms cycloalkyl in combination and l, m and n are each 0 or an integer of 1-3,

Rb is a hydrogen, an alkyl, an aralkyl, an aminoalkyl or a mono- or dialkylaminoalkyl; and

Rc is an optionally substituted heterocycle containing nitrogen,

an isomer thereof and/or a pharmaceutically acceptable acid addition salt thereof.

19. The use of claim 16, wherein the compound having a Rho kinase inhibitory activity is a compound selected from the group consisting of (+)-trans-4-(1-aminoethyl)-1-(4-pyridylcarbamoyl)cyclohexane, (+)-trans-N-(1H-pyrrolo[2,3-b]pyridin-4-yl)-4-(1-aminoethyl)cyclohexanecarboxamide, (R)-(+)-N-(4-pyridyl)-4-(1-aminoethyl)benzamide and (R)-(+)-N-(1H-pyrrolo[2,3-b]pyridin-4-yl)-4-(1-aminoethyl)benzamide, and/or a pharmaceutically acceptable acid addition salt thereof.

20. The use of claim 16, wherein the compound having a Rho kinase inhibitory activity is a (+)-trans-4-(1-aminoethyl)-1-(4-pyridylcarbamoyl)cyclohexane, and/or a pharmaceutically acceptable acid addition salt thereof.

(amended)

21. A commercial package comprising a pharmaceutical composition for the prophylaxis and treatment of interstitial pneumonia and pulmonary fibrosis of any of claim 6 ~~to claim 10~~, and a written matter associated therewith, the written matter stating that the pharmaceutical composition can or should be used for the prophylaxis and treatment of interstitial pneumonia and pulmonary fibrosis.